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L2 ANSWER 1 OF 2 MEDLINE on STN DUPLICATE 1
AN 2001664325 MEDLINE
DN PubMed ID: 11518704
TI IRAK-mediated translocation of TRAF6 and TAB2 in the interleukin-1-induced activation of NFkappa B.
AU Qian Y; Commane M; Ninomiya-Tsuji J; Matsumoto K; Li X
CS Department of Immunology, Lerner Research Institute, the Cleveland Clinic Foundation, Cleveland, Ohio 44195, USA.
NC GM 600020 (NIGMS)
SO Journal of biological chemistry, (2001 Nov 9) 276 (45) 41661-7.
Journal code: 2985121R. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200112
ED Entered STN: 20011119
Last Updated on STN: 20030105
Entered Medline: 20011205
AB The interleukin-1 (IL-1) receptor-associated kinase (IRAK) is required for the IL-1-induced activation of nuclear factor kappaB and c-Jun N-terminal kinase. The goal of this study was to understand how IRAK activates the intermediate proteins TRAF6, TAK1, TAB1, and TAB2. When IRAK is phosphorylated in response to IL-1, it binds to the membrane where it forms a complex with TRAF6; TRAF6 then dissociates and translocates to the cytosol. The membrane-bound IRAK similarly mediates the IL-1-induced translocation of TAB2 from the membrane to the cytosol. Different regions of IRAK are required for the translocation of TAB2 and TRAF6, suggesting that IRAK mediates the translocation of each protein separately. The translocation of TAB2 and TRAF6 is needed to form a TRAF6-TAK1-TAB1-TAB2 complex in the cytosol and thus activate TAK1. Our results show that IRAK is required for the IL-1-induced phosphorylation of **TAK1**, **TAB1**, and **TAB2**. The phosphorylation of these three proteins correlates strongly with the activation of nuclear factor kappaB but is not necessary to activate c-Jun N-terminal kinase.

L2 ANSWER 2 OF 2 MEDLINE on STN DUPLICATE 2
AN 2000167218 MEDLINE
DN PubMed ID: 10702308

TI TAK1 mitogen-activated protein kinase kinase kinase is activated by autophosphorylation within its activation loop.

AU Kishimoto K; Matsumoto K; Ninomiya-Tsuji J

CS Department of Molecular Biology, Graduate School of Science, Nagoya University and CREST, Japan Science and Technology Corporation, Chikusa-ku, Nagoya 464-8602, Japan.

SO Journal of biological chemistry, (2000 Mar 10) 275 (10) 7359-64.
Journal code: 2985121R. ISSN: 0021-9258.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

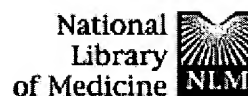
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FS Priority Journals

EM 200004

ED Entered STN: 20000413
Last Updated on STN: 20000413
Entered Medline: 20000403

AB TAK1, a member of the mitogen-activated kinase kinase kinase family, is activated in vivo by various cytokines, including interleukin-1 (IL-1), or when ectopically expressed together with the TAK1-binding protein TAB1. However, this molecular mechanism of activation is not yet understood. We show here that endogenous TAK1 is constitutively associated with TAB1 and phosphorylated following IL-1 stimulation. Furthermore, TAK1 is constitutively phosphorylated when ectopically overexpressed with TAB1. In both cases, dephosphorylation of TAK1 renders it inactive, but it can be reactivated by preincubation with ATP. A mutant of TAK1 that lacks kinase activity is not phosphorylated either following IL-1 treatment or when coexpressed with TAB1, indicating that TAK1 phosphorylation is due to autophosphorylation. Furthermore, mutation to alanine of a conserved serine residue (Ser-192) in the activation loop between kinase domains VII and VIII abolishes both phosphorylation and activation of TAK1. These results suggest that IL-1 and ectopic expression of TAB1 both activate TAK1 via autophosphorylation of Ser-192.



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Feedback control of the protein kinase TAK1 by SAPK2a/p38alpha.
EMBO J. 2003 Nov 3;22(21):5793-805.
PMID: 14592977 [PubMed - indexed for MEDLINE]

☐ 2: [Jang SB, Won J, Kim H, Kim J, Lee KH, Han H, Rha HK, Choi CR.](#)

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TAK1 mediates lipopolysaccharide-induced RANTES promoter activation in BV-2 microglial cells.
Mol Cells. 2002 Aug 31;14(1):35-42.
PMID: 12243350 [PubMed - indexed for MEDLINE]

☐ 3: [Kawahara T, Kuwano Y, Teshima-Kondo S, Sugiyama T, Kawai T, Nikawa T, Kishi K, Rokutan K.](#)

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Helicobacter pylori lipopolysaccharide from type I, but not type II strains, stimulates apoptosis of cultured gastric mucosal cells.
J Med Invest. 2001 Aug;48(3-4):167-74.
PMID: 11694956 [PubMed - indexed for MEDLINE]

☐ 4: [Kawahara T, Teshima S, Kuwano Y, Oka A, Kishi K, Rokutan K.](#)

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Helicobacter pylori lipopolysaccharide induces apoptosis of cultured guinea gastric mucosal cells.
Am J Physiol Gastrointest Liver Physiol. 2001 Sep;281(3):G726-34.
PMID: 11518685 [PubMed - indexed for MEDLINE]

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TAK1 is a ubiquitin-dependent kinase of MKK and IKK.
Nature. 2001 Jul 19;412(6844):346-51.
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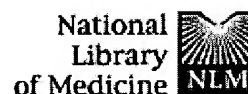
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TAB2 and TAB3 activate the NF-kappaB pathway through binding to polyubiquitin chains.
Mol Cell. 2004 Aug 27;15(4):535-48.
PMID: 15327770 [PubMed - indexed for MEDLINE]

☐ 2: Cheung PC, Campbell DG, Nebreda AR, Cohen P. Related Articles,

Feedback control of the protein kinase TAK1 by SAPK2a/p38alpha.
EMBO J. 2003 Nov 3;22(21):5793-805.
PMID: 14592977 [PubMed - indexed for MEDLINE]

☐ 3: Lynn DJ, Lloyd AT, O'Farrelly C. Related Articles,

In silico identification of components of the Toll-like receptor (TLR) signaling pathway in clustered chicken expressed sequence tags (ESTs).
Vet Immunol Immunopathol. 2003 Jun 20;93(3-4):177-84.
PMID: 12814703 [PubMed - indexed for MEDLINE]

☐ 4: Suzawa M, Takada I, Yanagisawa J, Ohtake F, Ogawa S, Yamauchi T, Kadowaki T, Takeuchi Y, Shibuya H, Gotoh Y, Matsumoto K, Kato S. Related Articles,

Cytokines suppress adipogenesis and PPAR-gamma function through the TAK1/TAB1/NIK cascade.
Nat Cell Biol. 2003 Mar;5(3):224-30.
PMID: 12598905 [PubMed - indexed for MEDLINE]

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TAB2 is essential for prevention of apoptosis in fetal liver but not for interleukin-1 signaling.
Mol Cell Biol. 2003 Feb;23(4):1231-8.
PMID: 12556483 [PubMed - indexed for MEDLINE]


☐ 6: Jiang Z, Ninomiya-Tsuji J, Qian Y, Matsumoto K, Li X. Related Articles,

Interleukin-1 (IL-1) receptor-associated kinase-dependent IL-1-induced signaling complexes phosphorylate TAK1 and TAB2 at the plasma membrane and act TAK1 in the cytosol.
Mol Cell Biol. 2002 Oct;22(20):7158-67.
PMID: 12242293 [PubMed - indexed for MEDLINE]


☐ 7: Wald D, Commene M, Stark GR, Li X. Related Articles,

IRAK and TAK1 are required for IL-18-mediated signaling.
Eur J Immunol. 2001 Dec;31(12):3747-54.
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☐ 8: Qian Y, Commene M, Ninomiya-Tsuji J, Matsumoto K, Li X. Related Articles,

 **IRAK-mediated translocation of TRAF6 and TAB2 in the interleukin-1-induced activation of NFkappa B.**
J Biol Chem. 2001 Nov 9;276(45):41661-7. Epub 2001 Aug 22.
PMID: 11518704 [PubMed - indexed for MEDLINE]


☐ **9:** [Wang C, Deng L, Hong M, Akkaraju GR, Inoue J, Chen ZJ.](#) [Related Articles,](#)




 **TAK1 is a ubiquitin-dependent kinase of MKK and IKK.**
Nature. 2001 Jul 19;412(6844):346-51.
PMID: 11460167 [PubMed - indexed for MEDLINE]

☐ **10:** [Holtmann H, Enninga J, Kalble S, Thiefes A, Dorrie A, Broemer M, Winzen R, Wilhelm A, Ninomiya-Tsuji J, Matsumoto K, Resch K, Kracht M.](#) [Related Articles,](#)

 **The MAPK kinase kinase TAK1 plays a central role in coupling the interleukin-1 receptor to both transcriptional and RNA-targeted mechanisms of gene regulation.**
J Biol Chem. 2001 Feb 2;276(5):3508-16. Epub 2000 Oct 24.
PMID: 11050078 [PubMed - indexed for MEDLINE]

☐ **11:** [Kishimoto K, Matsumoto K, Ninomiya-Tsuji J.](#) [Related Articles,](#)

 **TAK1 mitogen-activated protein kinase kinase kinase is activated by autophosphorylation within its activation loop.**
J Biol Chem. 2000 Mar 10;275(10):7359-64.
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